

## CLAIMS

What is claimed is:

1. A method of measuring the amount of an unlabeled organic acid in a sample, comprising:
  - a) adding to a sample suspected of containing the unlabeled organic acid to be measured an amount of an oxygen-18 labeled organic acid structurally similar or identical to the unlabeled organic acid to be measured, wherein said oxygen-18 labeled organic acid is not oxygen-18 labeled homovanillic acid or includes at least two oxygen-18 labeled organic acids;
  - b) processing the sample;
  - c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample; and
  - d) using the amount of oxygen-18 organic acid measured in step c) to adjust the amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.
2. The method of claim 1, wherein said detection is accomplished by mass spectrometry.
3. The method of claim 2, wherein said mass spectrometry is gas chromatography—mass spectrometry.
4. The method of claim 2, wherein said mass spectrometry is liquid chromatography—mass spectrometry.
5. The method of claim 1, wherein said 18-oxygen containing organic acid is a member selected from the group consisting of hydroxyl mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.
6. The method of claim 1, wherein said sample is a urine sample.

7. The method of claim 1 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.
8. The method of claim 1, wherein said processing results in chemical modification of the unlabeled organic acid.
9. A method of measuring the amount of at least one unlabeled organic acid in a sample, comprising;
  - a) adding to a sample suspected of containing the at least one unlabeled organic acid to be measured an amount of at least one oxygen-18 labeled organic acid selected from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid;
  - b) processing the sample;
  - c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample; and
  - d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the amount of a structurally similar or identical unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.
10. The method of claim 9 wherein at least two oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid are added to said sample.
11. The method of claim 9 wherein at least 3 or more oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid are added to said sample.
12. The method of claim 9 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.

13. The method of claim 9 wherein said processing results in chemical modification of the unlabeled organic acid.
14. The method of claim 9, wherein said detection is accomplished by mass spectrometry.
15. The method of claim 9, wherein said mass spectrometry is gas chromatography—mass spectrometry.
16. The method of claim 9, wherein said mass spectrometry is liquid chromatography—mass spectrometry.
17. The method of claim 9, wherein said sample is a urine sample.
18. A composition of oxygen-18 labeled organic acids for use as a standard to quantitatively determine the recovery of a structurally similar or identical organic acid, said composition comprising at least one oxygen-18 labeled organic acid selected from each of a hydroxyl mono-acid dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.
19. The composition of claim 18 wherein said hydroxyl mono-acid is selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxy isovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaproic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, homvanillic acid, indoleacetic acid and 3-hydroxydodecanoic acid.

20. The composition of claim 18 wherein said dihydroxy mono-acid is selected from the group consisting of glyceric acid, mevalonic acid, vanillymandelic acid and 4-hydroxyphenylacetic acid.
21. The composition of claim 18 wherein said dicarboxyl organic acid is selected from the group consisting of malonic acid, methylmelonic acid, succinic acid, ethylmalonic acid, methylsuccinic acid, glutaric acid, 3-methylglutaric acid, adipic acid, 3-methyl adipic acid, suberic acid, azelaic acid, sebacic acid and dodecanedioic acid.
22. The composition of claim 18 wherein said hydroxyl dicarboxyl acid is selected from the group consisting of malic acid, 2-hydroxyglutaric acid, 3-hydroxyglutaric acid, 3-hydroxy-3-methylglutaric acid, 2-hydroxyadipic acid, 3-hydroxyadipic acid and 3-hydroxysebacic acid.
23. The composition of claim 18 wherein said tricarboxyl acid is selected from the group consisting of isocitric acid, citric acid, methyl citric acid and aconitic acid.
24. The composition of claim 18 wherein said glycine conjugate is selected from the group consisting of propionylglycine, crotonylglycine, isobutyrylglycine, butyrylglycine, tiglylglycine, 3-methylcrotonylglycine, 2-methylbutyrylglycine, isovalerylglycine, valerylglycine, hexanoylglycine, hippuric acid, phenpropionylglycine and suberylglycine.
25. The composition of claim 18 wherein said oxo acid is selected from the group consisting of glyoxylic acid, pyruvic acid, 2-oxobutyric acid, acetoacetic acid, 2-oxoisovaleric acid, 5-oxoproline, 2-oxo-3-methylvaleric acid, 2-oxosocaproic acid, 2-oxoglutaric acid, succinylacetone, 2-oxoadipic acid, 3-oxoadipic acid, phenpyruvic acid, 4-hydroxyphenpyruvic acid and 2-methylacetoacetic acid.
26. The composition of claim 18 wherein said composition comprises two or more oxygen-18 organic acids from each of a dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.

27. The composition of claim 18 wherein said composition comprises two or more oxygen-18 organic acids from each of a dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.

28. A composition comprising a biological sample and a mixture of oxygen-18 labeled organic acids wherein said mixture comprises at least one oxygen-18 labeled organic acid selected from each of a hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.

29. The composition of claim 28 wherein said composition comprises two or more oxygen-18 organic acids from each of a hydroxyl mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid.

30. A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of an unlabeled organic acid in a sample of the individual, said method comprising:

a) adding to a sample from the individual an amount of an oxygen-18 labeled organic acid structurally similar or identical to the unlabeled organic acid to be measured, wherein said oxygen-18 labeled organic acid is not oxygen-18 labeled homovanillic acid or includes at least two oxygen-18 labeled organic acids;

b) processing the sample;

c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample;

d) using the amount of oxygen-18 organic acid measured in step c) to adjust the amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample; and

e) determining if the amount of the unlabeled organic acid detected in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

31. The method of claim 30 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.

32. The method of claim 30 wherein said processing results in chemical modification of the unlabeled organic acid.
33. The method of claim 30 wherein said detection is accomplished by mass spectrometry.
34. The method of claim 33 wherein said mass spectrometry is gas chromatography—mass spectrometry.
35. The method of claim 33 wherein said mass spectrometry is liquid chromatography—mass spectrometry.
36. The method of claim 30 wherein said sample is a urine sample.
37. A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of at least one unlabeled organic acid in a sample of the individual, said method comprising:
- a) adding to a sample from the individual an amount of at least one oxygen-18 labeled organic acid selected from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid;
  - b) processing the sample;
  - c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample;
  - d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the amount of a structurally similar or identical unlabeled organic acid measured in the processed sample so as to reflect the amount of the at least one unlabeled organic acid originally present in the sample; and
  - e) determining if the amount of the at least one unlabeled organic acid originally present in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

38. The method of claim 37 wherein at least two oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid are added to said sample.
39. The method of claim 37 wherein at least 3 or more oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and oxo acid are added to said sample.
40. The method of claim 37 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.
41. The method of claim 37 wherein said processing results in chemical modification of the unlabeled organic acid.
42. The method of claim 37 wherein said detection is accomplished by mass spectrometry.
43. The method of claim 42 wherein said mass spectrometry is gas chromatography—mass spectrometry.
44. The method of claim 42, wherein said mass spectrometry is LC mass spectrometry.
45. The method of claim 37 wherein said sample is a urine sample.